

1 INCREASED INTRAMUSCULAR FATTY INFILTRATION
2 WITHOUT DIFFERENCES IN LUMBAR MUSCLE CROSS-SECTIONAL AREA
3 DURING REMISSION OF UNILATERAL RECURRENT LOW BACK PAIN
4

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ABSTRACT

Lumbar muscle degeneration is a common feature in non-specific low back pain (LBP). It is hypothesized that degenerated muscles might compromise spinal stability and lead to further injury/pain. However, little is known about lumbar muscle morphometry after resolution of LBP. Therefore, this study investigated the extent of lumbar muscle atrophy and fatty infiltration in individuals who are at risk for a recurrence of LBP. Thirteen participants in remission of unilateral recurrent LBP were compared to 13 healthy controls, comparable for age, weight, length and level of physical activity. Total, lean muscle and fat cross-sectional area (CSA) of lumbar multifidus (MF), erector spinae (ES) and psoas (PS) were investigated on T1-weighted Magnetic Resonance Imaging (MRI), bilaterally and at 3 lumbar levels (L3 upper, L4 upper and L4 lower endplate). In addition, a muscle-fat-index (MFI) was calculated reflecting the amount of fatty infiltration in lean muscle tissue. No significant differences for total, lean muscle and fat CSA were found between people in remission of recurrent LBP and the control group. Conversely, MFI was increased bilaterally at the 2 lowest lumbar levels. There were no differences between the previously painful and non-painful side of the LBP group for any of the parameters. These results show a generalized increase in intramuscular fatty infiltration in lean muscle tissue in the absence of macroscopical signs of muscle degeneration after resolution of LBP. These findings reflect a decreased muscle quality, but not quantity, and might indicate a pathophysiological mechanism contributing to recurrence of LBP.

42 KEY WORDS

43 Magnetic resonance imaging; recurrent low back pain; trunk muscles; muscle atrophy

Lumbar muscle degeneration is a common feature in non-specific low back pain (LBP) and is macroscopically characterized by decreased muscle size (atrophy) and increased fat deposition (Parkkola et al., 1993; Danneels et al., 2000). Lumbar muscle degeneration may compromise spinal stability and jeopardize spinal health, potentially leading to further injury/LBP (Panjabi, 1992). Consequently, lumbar muscle morphometry has been investigated increasingly as a biomarker of LBP.

Atrophy of the paraspinal muscles (especially multifidus [MF]) has been consistently demonstrated with LBP (Hultman et al., 1993; Hides et al., 1994; Danneels et al., 2000; Hides et al., 2008; Wallwork et al., 2008), and is often accompanied by reduced cross-sectional area (CSA) of the psoas (PS) muscle (Parkkola et al., 1993; Kamaz et al., 2007). With unilateral LBP distribution, atrophy of MF (Hyun et al., 2007; Hides et al., 2008; Kim et al., 2011) and PS (Barker et al., 2004; Ploumis et al., 2010) was more pronounced on the painful compared to the non-painful side. Results on fatty infiltration in relation to LBP are variable with fatty infiltrates observed in some studies (Hultman et al., 1993; Parkkola et al., 1993; Mengiardi, 2006; Kjaer et al., 2007), but not others (McLoughlin et al., 1994; Danneels et al., 2000; Kjaer et al., 2007).

Little however is known about lumbar muscle morphometry in individuals with a history of LBP but without current pain. Lumbar muscle degeneration after a LBP episode may be a pathophysiological mechanism for LBP recurrence. Hultman et al. (1993) found no differences in paraspinal CSA or density (=substitute for fatty infiltration) on CT (Computed Tomography) during remission of intermittent LBP

compared to healthy controls. Hides et al. (1996) prospectively investigated MF asymmetry between painful and non-painful sides during resolution of unilateral LBP using ultrasound: MF atrophy on the painful side did not recover automatically. Further research is warranted to characterize lumbar muscle degeneration during remission of LBP, when people are at risk of recurrent episodes.

Typically, lumbar muscle size (CSA) is measured by outlining fascial muscle borders on axial images (Hu et al., 2011), however, CSA measures may be distorted by replacement of muscle with adipose or connective tissue (Parkkola et al., 1993;Ropponen et al., 2008). Fat deposition is usually estimated qualitatively using visual grading systems (Kader et al., 2000;Ropponen et al., 2008), but these potentially overlook small changes in muscle composition (Mengiardi, 2006;Lee et al., 2008). Another approach is to distinguish muscle and fat tissue quantitatively (Ropponen et al., 2008;Hu et al., 2011). In that context, Magnetic Resonance Imaging (MRI) is preferred over CT, due to superior spatial resolution and distinguishing features of soft tissues without radiation exposure (Hu et al., 2011). A histographic method has been proven effective to separate muscle from clearly visible fat depositions based on differences in pixel signal intensity (SI)(Hyun et al., 2007;Lee et al., 2008;Min et al., 2009). The muscle-fat-index (MFI) is another method for interindividual comparison of intramuscular fatty infiltration, involving the calculation of the ratio of the mean SI in a region of muscle tissue relative to the SI in a homogenous region of fat (Elliott et al., 2005;Elliott et al., 2008b;Cagnie et al., 2009;Elliott et al., 2010).

Combining the measures total, lean muscle and fat CSA and MFI with MRI provides a quantitative and multifaceted view, to investigate whether lumbar muscle

89 morphometry and composition differs during remission of unilateral recurrent LBP
90 compared to a healthy control group, and whether this is pain-side related. We
91 hypothesised that lumbar muscle degeneration would be present in participants with a
92 history of LBP, and being most prominent on the previously painful side.

METHODS

Participants

Thirteen individuals with recurrent non-specific LBP were recruited via advertisement in the local community and university. Inclusion criteria were a history of at least 2 previous episodes of LBP (onset >6 months) that interfered with activities of daily living and/or required treatment (LBP characteristics: Table 1). Episodes were defined as bouts of LBP for a minimum of 24 hours, preceded and followed by a period of minimum 1 month without symptoms (de Vet et al., 2002). Testing was scheduled at least 1 month after the end of the previous episode (time since last episode: $64 \pm 33,6$ days).

Thirteen individuals without a history of LBP, comparable for gender, age, weight, length and level of physical activity, formed a healthy control group (demographic characteristics: Table 2).

Participants were excluded from either group if they reported: central, bilateral or variable localization of LBP; pain elsewhere in the body; lumbar muscle training in the past year; spinal deformities or surgery; task-limiting medical conditions or contra-indications for MRI.

After notification of the study procedures, which were approved by the local Ethics Committee, participants provided written informed consent.

Imaging procedures

T1-weighted images were acquired using a 3-Tesla MRI-scanner (Magnetom Trio-Tim, SyngoMR VB15 software, Siemens AG®, Erlangen Germany). Participants were placed

supine with a foam wedge supporting the legs (~30° hip flexion). A flexible 6-element body-matrix coil, centered ventrally on L4, was combined with the standard phased-array spine coil dorsally as a receiver-coil combination.

On a sagittal localizing scan, 3 slices were positioned as axially as possible along the upper endplate of L3 and L4 and lower endplate of L4, visualizing lumbar MF, erector spinae (ES) and PS. These levels were selected as paraspinal and PS muscle mass is at or near maximal, enhancing the possibility to demonstrate CSA differences (Danneels et al., 2000; Lee et al., 2008). Level L4 lower endplate was used as a substitute for L5, because the inclination of L5 is often too large to visualize the muscles' cross-section appropriately.

A spin-echo (SE) sequence was used: repetition time (TR) 550ms, echo time (TE) 9ms, acquisition matrix 384*258mm², flip angle 75°, field of view (FOV) 340mm, voxel size 0.9*0.9*4mm², scan time 4min45s.

Data analysis

MRI-data were analyzed using Image J (Java-based version of the public domain NIH Image Software; Research Services Branch), blind to the participants' LBP history. MF, ES and PS were bilaterally outlined at each level (=total muscle region of interest [ROI])(Fig. 1). Each ROI was then segmented based on differences in SI between fat and muscle tissue. Using a histogram showing the SI distribution, pixels with high SI (fat) were eliminated. From the remaining pixels (=lean muscle ROI)(Fig. 1), the mean SI was calculated. Total and lean muscle CSA (mm²) were calculated as the number of pixels in the respective ROI multiplied by the pixel size. Fat CSA was calculated as the

difference between total and lean muscle CSA. All CSAs were normalized to the vertebral body at the L4 upper endplate (Danneels et al., 2000).

Finally, the mean SI was calculated in a homogenous region of fat (lateral corner between right ES and quadratus lumborum). MFI was calculated by dividing the mean SI of the lean muscle ROI by the fat ROI (Elliott et al., 2005). Quantitative evaluation of paraspinal muscle composition on MRI has been proven highly reliable (Ropponen et al., 2008; Hu et al., 2011).

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics 19.

Descriptive statistics were calculated for participant and LBP characteristics. Between-group comparisons were tested using independent samples t-tests.

Total and lean muscle CSA, fat CSA and MFI were compared 1) between LBP and healthy control group (Group) and 2) between sides within the LBP group (Pain side) using linear mixed model analysis. These mixed models account for correlated measures by including a random intercept for participants, and adjust for Muscle (MF, ES, PS), Level (L3upper, L4upper, L4lower) and Body Side (left, right). Parameter estimation was done by restricted maximum likelihood. As differences between body sides, levels or muscles were not our main research questions, only main/interaction effects for Group and Pain side are presented. To rule out a possible influence of hand dominance, two left-handed participants were omitted from the mixed model analysis (11P-13C).

The association between CSA and MFI versus demographic and LBP variables was evaluated using Pearson's correlation coefficients.

160 Post-hoc comparisons were made when required and were adjusted using Bonferroni-
161 correction. Statistical significance was set at $\alpha=0.05$.

RESULTS

Differences between LBP and control group

For total muscle CSA, there was an interaction between Group and Muscle ($p=0.001$).

Post-hoc tests for individual muscles, revealed no group differences for any muscles at any levels (MF $P=0.337$; ES $P=0.627$; PS $P=0.339$)(Fig. 2, Table 3).

Similarly, there were no group differences for any muscles at any levels for lean muscle CSA (interaction Group*Muscle: $p=0.001$, Post hoc: MF $P=0.276$; ES $P=0.752$; PS $P=0.342$)(Fig. 2, Table 3).

There were no differences in fat CSA between the LBP and control group (main effect Group: $p=0.640$)(Fig. 2, Table 3).

MFI (interaction Group*Level: $p=0.005$) was higher in the LBP compared to the control group for all muscles at L4upper ($P=0.014$) and L4lower ($P=0.017$), but not at L3upper ($P=0.380$)(Fig. 3, Table 3).

Differences between previously painful and non-painful sides in the LBP group

There were no pain-side related differences in the LBP group for any muscles at any levels (Table 4): total and lean muscle CSA, fat CSA (Main effect Pain side respectively $p=0.581$; $p=0.418$; $p=0.353$), and MFI (Interaction effect Muscle*Pain side: $p<0.001$; Post Hoc: MF $P=0.932$; ES $P=0.153$; PS $P=0.585$).

Correlations

With regard to demographic characteristics, total and lean CSA correlated ($p<0.05$) with weight (respectively $r=0.578$; $r=0.529$), length (respectively $r=0.503$; $r=0.454$) and

183 body mass index (BMI)(respectively $r=0.496$; $r=0.456$). MFI correlated with weight
184 ($r=0.509$, $p=0.013$) and BMI ($r=0.553$, $p=0.006$).
185 Analysis of LBP characteristics showed that MFI correlated with the frequency of
186 episodes ($r=0.671$, $p=0.034$) and lean and total CSA were associated with the elapsed
187 time since the last episode (respectively $r=0.789$, $p=0.035$; $r=0.800$, $p=0.031$).

DISCUSSION

This study investigated whether lumbar muscle degeneration was present during remission of unilateral recurrent LBP. In contrast to our hypothesis, there were no differences in total, lean muscle or fat CSA from the control group, or pain-side related differences in the LBP group. Conversely, MFI was higher in the LBP group for all muscles (MF, ES, PS), without any pain-side related differences.

There were no group or pain-side related differences in muscle size for any muscles. The lack of group differences in the current study supports the results of Hultman et al. (1993), who showed no alterations in paraspinal (MF+ES) muscle CSA at L3 during remission of intermittent LBP. The lack of side differences in CSA differs however with the results of Hides et al. (1996), who reported ongoing MF atrophy on the painful side despite LBP resolution. This discrepancy may be related to methodological differences. First, in the study of Hides et al. MF CSA asymmetry was localized to the symptomatic level, while it was symmetric at the neighboring asymptomatic levels. In our study, the symptomatic level could not be evaluated because the population was recruited in remission of LBP. Moreover, MF asymmetry was principally reported at L5 and our study did not measure below the L4 lower endplate. In addition, measuring methods differed, ultrasound vs. MRI. Although these techniques previously yielded similar results for lumbar muscle CSA, it has not been demonstrated whether this holds in fatty infiltrated muscles (Hides et al., 1995). Finally, lumbar muscle size during

recovery of LBP was not directly compared to a control group (Hides et al., 1996), therefore group differences cannot be discussed.

Unlike other studies reporting atrophy during LBP (Parkkola et al., 1993;Hides et al., 1994;Danneels et al., 2000;Barker et al., 2004), we were not able to reveal differences in total or lean muscle CSA during remission of recurrent LBP. We speculate that muscle size was not reduced, or, had recovered in this specific population. Support for recovery from atrophy is provided by associations showing that 62 and 64% ($R^2=0.623$; $R^2=0.640$) of the variance in lean and total CSA, respectively, can be explained by the time elapsed between testing and previous LBP episode (mean: 64, min: 31, max: 144 days). This finding appears in contrast to Hides et al. (1996), who observed no alteration in localized MF asymmetry after about 42 pain-free days. In addition to the methodological differences discussed above, our association was irrespective of pain side, muscle or level and observed in a wider timeframe. Further longitudinal research of the natural course of lumbar muscle morphometry during resolution of LBP is needed.

Below, several hypotheses for decreased lumbar muscle size in relation to LBP are discussed in view of our lack of atrophy during remission of LBP. First, atrophy may result from muscular disuse e.g. general deconditioning and local disuse (altered recruitment)(Hides et al., 1994;Danneels et al., 2000;Hodges et al., 2006). With regard to conditioning status, both groups had similar scores for physical activity, comparable to scores from young adults (Baecke et al., 1982). Altered recruitment of muscles cannot be discounted as there is evidence for decreased (Macdonald et al., 2009), unchanged (Macdonald et al., 2010) and increased (Macdonald et al., 2011;D'Hooze et al., 2012a)

MF recruitment during remission of recurrent LBP. Second, experimentally-induced spinal injury (disc and nerve root lesion) has been shown to cause specific patterns of muscle wasting in the porcine MF within 3 days of the lesion (Hodges et al., 2006). It is not known what muscular replications can particularly be expected from *non-specific* LBP, 64 days at average after LBP resolution. Third, if peripheral nociception would reduce muscle CSA directly, this could contribute to marked differences observed during LBP compared to less conclusive evidence during LBP remission. Further research that investigates the isolated effect of nociception on lumbar muscle size may be able to confirm this hypothesis.

MFIs in lean muscle tissue were increased during remission of LBP, which reflects increased relative amounts of intramuscular lipids (Elliott et al., 2010). The extent of lean fatty infiltration was generalized rather than localized (multiple muscles and levels, both previously painful and non-painful sides).

The main causes of fatty infiltration are muscular disuse and spinal injury, similar to the causes of atrophy (Elliott et al., 2006;Hodges et al., 2006). Although the generalized effect in MFI appears in favour of the deconditioning-hypothesis, this is not supported by similar scores for physical activity in both groups. Further, because paraspinal and PS muscles have different nerve supplies (dorsal vs. ventral rami of lumbar nerves, respectively) and MFI is increased bilaterally, denervation is not considered a plausible explanation in the current study. Finally, the positive correlation between fatty infiltration and episode frequency (mean: 4.4, min: 2, max: 9 per year; $R^2=0.450$), may suggest a role for nociception in fatty infiltration. This assumption is consistent with

previous observations of generalized inhibition of MF, ES and PS recruitment with experimentally-induced pain (Dickx et al., 2008;D'Hooze et al., 2012b). Further research is required to determine if peripheral nociception is involved in fatty infiltration via a reflex-mediated decrease in neural drive.

Previously, Hultman et al. (1993) found no difference in paraspinal muscle density on CT during remission of intermittent LBP. Results of fatty infiltration in the presence of LBP are less consistent than CSA measures. Some authors demonstrate increased fatty infiltration (Parkkola et al., 1993;Mengiardi, 2006;Kjaer et al., 2007; Hultman et al., 1993), whereas others show no difference to healthy controls (McLoughlin et al., 1994;Danneels et al., 2000;Kjaer et al., 2007). The discrepancy in results may be due to methodological differences such as the ROI in which fatty infiltration is determined (total vs. lean muscle, isolated MF vs. paraspinals grouped) or measuring technique (qualitative vs. quantitative, CT vs. MRI). The current study measured fatty infiltration in two complementary modes yielding divergent results: lean fatty infiltration was increased, without macroscopic alterations. Similarly, Mengiardi et al. (2006) revealed increased metabolic fat content with proton MR spectroscopy, which was not detectable with a semi-quantitative visual grading system using conventional MRI.

Using a multifaceted approach to investigate lumbar muscle structure, the current study showed that fatty infiltration in lean muscle tissue was increased, without alterations in muscle size or macroscopic fat deposition during remission of LBP. This emphasises the importance of differentiating muscle quantity (CSA) and quality (composition). In this respect, Elliott et al. reported enlarged cervical muscle CSAs and

fatty infiltration in relation to whiplash-associated disorders, acknowledging that caution must be exercised during interpretation of CSA measurements in the presence of intramuscular fat (Elliott et al., 2008a;Elliott et al., 2010). Similarly, lean fatty infiltration may be masking a reduction in muscle size in our results.

It is assumed that fatty infiltration may negatively affect muscle contractility when muscle fibers are replaced with non-contractile tissue. Consequently, the deteriorated muscle composition may contribute to LBP recurrence. This adds to the existing evidence of lumbar muscle dysfunction during remission of recurrent LBP (Macdonald et al., 2009-2010-2011;D'Hooge et al., 2012a).

There are some limitations to this study. The absence of differences in CSA between groups or sides may be related to small participant numbers. Further studies with larger sample size are required to confirm our findings. The MFI has not previously been applied in the lumbar region. The index has been used extensively in the cervical spine (Elliott et al., 2005;Elliott et al., 2006). Unlike the cervical region, the fat ROI could not be drawn in a clear intermuscular fat area, but instead, peripherally from the lumbar muscles. This yielded comparable but slightly lower indices (range: 0.15-0.30), which might be due to calculating the MFI after segmentation of visible fat.

In conclusion, the current study shows a generalized increase in fatty infiltration in lean lumbar muscle tissue, in the absence of alterations in muscle size or macroscopic fat deposition after resolution of LBP. It is hypothesized that decreased muscle quality may contribute to recurrence of LBP.

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407 TABLES

408 **Table 1:** LBP characteristics (Mean \pm SD)

| Variable | |
|--|-----------------|
| Duration since first onset LBP (months) | 109 \pm 70 |
| Frequency of episodes (per year) | 4.4 \pm 2.0 |
| Duration of episode (days) | 5.5 \pm 3.7 |
| Pain intensity during episode (NRS, 0-100) | 57.4 \pm 12.7 |
| Disability during episode (NRS, 0-100) | 45.8 \pm 21.0 |

SD – standard deviation

LBP – low back pain

NRS – numeric rating scale

409 **Table 2:** Participant demographics (Mean \pm SD)

| Variable | LBP group | Control group | p-value |
|------------------|-------------------|-------------------|---------|
| n | 13 | 13 | - |
| Male : female | 6 : 7 | 6 : 7 | - |
| Age (years) | 32.09 \pm 11.52 | 32.13 \pm 10.57 | 0.993 |
| Body weight (kg) | 74.62 \pm 15.31 | 74.89 \pm 13.28 | 0.962 |
| Body length (m) | 177.96 \pm 9.20 | 176.62 \pm 8.60 | 0.703 |
| Baecke-score | 8.55 \pm 1.25 | 8.62 \pm 1.34 | 0.896 |

SD – standard deviation

LBP – low back pain

410 **Table 3:** Means (SD) for total and lean muscle CSA, fat CSA and MFI for the LBP and
 411 control group per muscle, adjusted for body side and level

| Parameter | Muscle | LBP | Control |
|------------------|--------|-------------|-------------|
| | | group | group |
| total muscle CSA | MF | 41.0 (15.7) | 37.5 (19.1) |
| | ES | 96.1 (14.1) | 99.4 (16.2) |
| | PS | 79.8 (17.6) | 73.0 (19.1) |
| lean muscle CSA | MF | 34.6 (12.7) | 30.6 (17.5) |
| | ES | 87.1 (15.1) | 89.5 (17.6) |
| | PS | 75.3 (16.5) | 68.8 (19.0) |
| fat CSA | MF | 6.5 (3.6) | 6.8 (4.2) |
| | ES | 8.4 (2.1) | 10.0 (2.9) |
| | PS | 4.6 (1.7) | 4.2 (2.8) |
| MFI | MF | 18.4 (6.4) | 14.0 (2.6) |
| | ES | 23.9 (6.1) | 20.7 (2.5) |
| | PS | 25.9 (5.9) | 21.9 (2.9) |

SD – standard deviation

LBP – Low back pain

CSA – cross-sectional area ; MFI – muscle-fat-index

MF – multifidus; ES – erector spinae; PS - psoas

Table 4: Means (SD) for total and lean muscle CSA, fat CSA and MFI on the previously painful (Pain) and non-painful (No Pain) side in the LBP group per muscle, adjusted for body side and level

| Parameter | Muscle | No Pain | Pain |
|------------------|--------|-------------|-------------|
| total muscle CSA | MF | 40.9 (15.7) | 41.0 (15.5) |
| | ES | 96.1 (14.0) | 96.0 (13.8) |
| | PS | 81.5 (17.7) | 78.2 (17.5) |
| lean muscle CSA | MF | 34.9 (12.6) | 34.3 (12.4) |
| | ES | 87.0 (15.1) | 87.3 (14.9) |
| | PS | 77.6 (16.6) | 72.9 (16.4) |
| fat CSA | MF | 6.3 (3.6) | 6.7 (3.7) |
| | ES | 8.6 (2.0) | 8.2 (2.1) |
| | PS | 4.0 (1.6) | 5.2 (1.7) |
| MFI | MF | 18.8 (6.3) | 18.1 (6.8) |
| | ES | 22.1(5.9) | 25.7 (6.5) |
| | PS | 27.0 (6.0) | 24.9 (6.1) |

SD – standard deviation

LBP – Low back pain

CSA – cross-sectional area ; MFI – muscle-fat-index

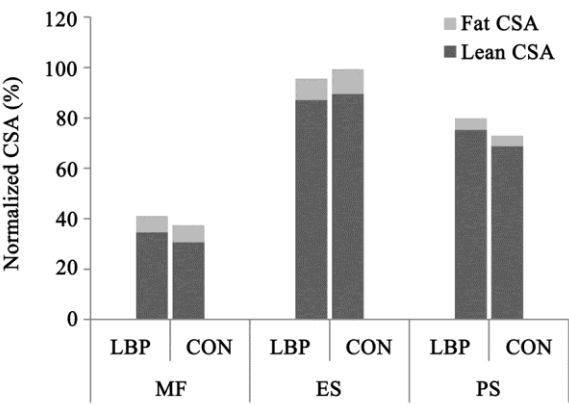
MF – multifidus; ES – erector spinae; PS - psoas

417 **Figure 1:** Axial slice at the level of L4 upper endplate. Lean cross-sectional area (CSA)
418 is illustrated on the left; total CSA is illustrated on the right for multifidus, erector
419 spinae and psoas in a representative participant from the LBP group.



420

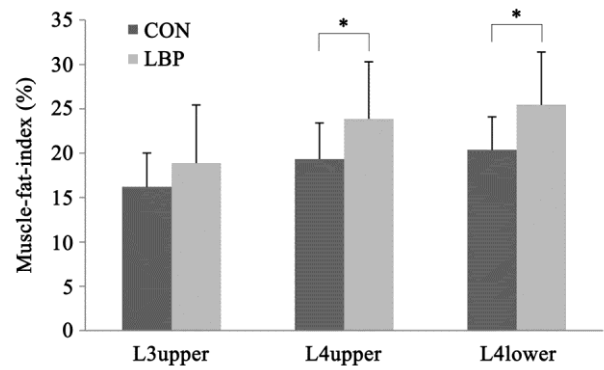
421 **Figure 2:** Normalized lean and fat cross-sectional area (CSA, %) per muscle (MF =
422 multifidus, ES = erector spinae, PS = psoas) for low back pain (LBP) and control (CON)
423 group. Total CSA is represented as the sum of lean and fat CSA.



424

425 **Figure 3:** Muscle-fat-index per lumbar level for low back pain (LBP) and control (CON)
426 group. * $p<0.05$

427



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